A Tribute to Hugh de Wardener

We note with sadness the death of Hugh de Wardener on September 29, 2013 at the age of 98. He was truly a pioneer and early developer of the specialty of Nephrology whose seminal contributions have been well described recently by Schrier.1 To us, he was a creative and inspirational innovator in the field to which we devoted most of our investigative effort during our career—the search for a natriuretic hormone. As our final tribute to him, we would like to recognize his seminal contributions to that field and offer our brief assessment of the long-term importance of those contributions.

In a 1957 review of the literature, Smith2 postulated the existence of a humoral substance that controlled renal sodium excretion. Smith speculated that this sodium-regulating hormone was analogous to the free-water–regulating antidiuretic hormone, and hence it was an antinatriuretic hormone. Four years later, in 1961, de Wardener et al3 demonstrated a transferrable natriuretic factor in cross-circulated blood from volume-expanded dogs to euvolemic dogs and proposed the existence of a natriuretic hormone. This provocative article led to an explosion of investigative activity and established de Wardener as the pioneer of the field.

Although these initial experiments were careful to control blood volume in the recipient dogs, they did not entirely control for changes in the composition of blood by the volume expansion. This was quickly recognized and led to a burst of studies on the role of what came to be known as physical factors on renal sodium excretion. The influence of these factors hung over further attempts to demonstrate a natriuretic hormone until 1967 when de Wardener’s laboratory published further studies using a revised protocol. In these, the composition of blood used to expand the recipient dog was carefully controlled by mixing in a reservoir or by cross-circulation with a donor dog.4 The results, quickly confirmed in several laboratories using an assortment of variations on de Wardener’s protocol, supported the search for a natriuretic hormone, although not without continued controversy to be sure.

One of de Wardener’s major contributions was a series of review articles, in which his lucid logic, clarity of expression, and ability to synthesize a large and disparate literature were influential—as he stated in one of those reviews5: “The suggestion that….there is a circulating substance other than aldosterone which controls sodium excretion was at first totally ignored and then vigorously denied. It was considered by some that the discovery of these physical factors automatically ruled out any other possibility.” The effect of his logical arguments and the weight of his prestige on the development of the field after his initial experiments cannot be overemphasized.

As with any pioneering observation, the search for a natriuretic hormone led to many unexpected developments. The hypothesis that natriuretic hormone might increase sodium excretion by inhibiting renal tubular Na, K ATPase, which emerged soon after de Wardener’s original experiments, led directly to the surprising discovery of mammalian endogenous digitalis-like factors. The discovery that inhibition of the sodium pump in vascular tissue caused vasoconstriction, and elucidation of the mechanism of this effect, led directly to the major hypothesis that endogenous digitalis-like factors participate in the pathophysiology of various forms of hypertension. Thus, a causal mechanism linking renal regulation of salt and water balance to control of blood pressure was elucidated. de Wardener was an early, enthusiastic proponent of this hypothesis and published several articles supporting it. In addition, he wrote several outstanding reviews laying out its details.6–9 Elucidation of the structure of the several digitalis-like factors, their many effects beyond inhibition of the sodium pump, and their role in physiology and pathophysiology are the subject of much ongoing investigation.

de Wardener’s work also laid the groundwork for the discovery of the atrial natriuretic peptides. Interestingly, discovery of these peptides was a convergence of the search for volume-regulated natriuretic hormones with the search for volume receptors, one of which was thought to be the cardiac atria. Soon after their detection, it was shown that atrial peptides were not inhibitors of Na, K ATPase in a digitalis-like mechanism, but were vasodilators, and their ability to cause natriuresis was probably not their most important property. Thus, despite the importance of their discovery, the brilliance of the science, and the widespread, intense interest in atrial peptides, de Wardener maintained his focus on the search for a Na, K ATPase inhibitor natriuretic hormone.

We enjoyed extensive personal interactions with de Wardener in a variety of settings during our years of active investigation. These included many professional society meetings as well as satellite symposia, several of which we were
privileged to organize. One of these satellite meetings was organized by de Wardener himself with his colleague Graham MacGregor in London after the 10th International Congress of Nephrology in July of 1987. In addition, we were honored to have him visit our several institutions as a visiting professor, where he entertained us with his charm, enthusiasm, and delightful personality. He was a seasoned world traveler, and it is remarkable how he has accomplished so much while maintaining such an ambitious travel schedule.

The world of cardiovascular-renal investigation has lost one of its premier contributors. We will miss Hugh de Wardener; however, we will treasure the memories of the scientific and social interactions with him.

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