Last Word on Counterpoint: Activation of the intrarenal renin-angiotensin system is the dominant contributor to systemic hypertension

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TO THE EDITOR: It is invigorating to see so much interest in our Point:Counterpoint debate concerning the “dominant contributor to hypertension.” From the comments provided by the various contributors (see Ref. 2), it is obvious that we are still a long way from clearly delineating the “dominant contributor.” In my article, I provided evidence supporting the critical roles of the kidneys and the pivotal influence of the intrarenal renin-angiotensin system (RAS). As discussed, a single mutation causing overexpression or increased activity in any one of several critical sodium transporters in the kidney is able to cause hypertension (4), thus providing proof of principle that a single gene disorder altering sodium excretion can cause hypertension. Furthermore, the unique characteristics of the intrarenal RAS, when inappropriately stimulated, exert pleiotropic effects on the kidney that can elicit sustained vasoconstrictor stimulus to the renal microcirculation via both direct actions and increased sensitivity of the tubuloglomerular feedback mechanism as well as direct stimulation of sodium transport in proximal and distal nephron segments (3, 5). Thus, even when a specific derangement in kidney transport function is not directly responsible for the hypertension, the failure to appropriately suppress the intrarenal RAS provides a permissive role. Nevertheless, as pointed out in the many thoughtful comments in the commentaries (2), it is clear that no single organ or endocrine system can be considered as being responsible for all types of hypertension. It is likely that precipitating functional derangements can originate from almost any part of the body including the brain, vasculature, and endocrine systems as well as the kidneys. In essence, arterial blood pressure is simply an easily accessible window into the cardiovascular system, and hypertension is a sign that there is a dysfunction in one or more of the homeostatic mechanisms regulating blood pressure. There are indeed many types of vascular, endocrine, neural, and renal derangements that can serve as the initial stimulus which ultimately is reflected as an elevated arterial pressure. Nevertheless, my rationale for emphasizing the cardinal role of the kidneys, and particularly of the intrarenal RAS, is that ultimately, a sustained inappropriate alteration in kidney function is requisite for the maintenance of hypertension (5). When the initiating factor is of renal origin and there is an inappropriate level of activity of the intrarenal RAS, it appears that the systemic compensatory mechanisms are not sufficient to overcome the hypertensinogenic influence and an elevated arterial pressure must develop to allow restoration of sodium balance (1). Alternatively, when the initiating stimulus originates in a non-kidney locus, such as vascular endothelial dysfunction or increased sympathetic activity, altered kidney function must be part of the syndrome because when the intrarenal RAS responds appropriately to an extrarenal hypertensinogenic stimulus, the long-term hypertensive effects will be blunted. If the intrarenal RAS is inappropriately activated, altered kidney function becomes permissive for the maintenance of hypertension. In either case, it is difficult to escape the conclusion that the kidneys play the pivotal role in the pathophysiology of hypertension (5).

REFERENCES