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## **A new look at the mosaic theory of hypertension**

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Despite extensive research, the pathogenesis of hypertension is still elusive. While the origin is known in less than 5% of patients, the majority of patients have primary hypertension, where identifiable cause(s) remain unknown. However, what is clear is that the pathophysiology of primary hypertension is multifactorial, multifaceted, highly complex and includes several interacting physiological systems. This was already highlighted over 70 years ago (1), when Irving H. Page suggested in his 'mosaic theory' that hypertension is a disease of 'dysregulation' that involves multiple interacting elements (Black elements, Figure). This was subsequently conceived as an octagon with regulators on each point, connected by arrows. This paradigm was refined 32 years later (2) to include genetic, environmental, anatomical, adaptive, neural, endocrine, humoral and hemodynamic factors as the pivotal components of the octagon (Blue elements, Figure).

Since then there has been enormous progress in unravelling molecular, cellular and organ system mechanisms that underlie hypertension. Moreover it has become evident that the development of primary hypertension, from early to established and advanced stages, involves a range of cardiovascular and renal mechanisms ranging from the dysregulation of fetal/neonatal renal programming, the elevation in cardiac output that is characteristic of the elevations in blood pressure in adolescents and young adults to the increased peripheral resistance that is the hallmark of established and advanced hypertension.

With advancements in hypertension research, it has become necessary to reconsider the comprehensiveness of the hypertension mosaic. This was highlighted in 2013 in a paper entitled 'The mosaic theory revisited' (3). In the current issue, we further

develop the concept with a collection of reviews focusing on some new aspects (Red elements, Figure) related to: genomics (4), sex hormones (5), the sympathetic nervous system (6), the brain aminopeptidase system (7), hyperinsulinemia and insulin resistance (8), oxidative stress (9), inflammation (10), the angiotensin AT2 receptor (11) and structure, mechanics and function of the vasculature (12).

This compendium of reviews, together with the two papers on hypertension guidelines (13,14), provides state-of-the art knowledge that will keep the reader abreast of the complexities associated with hypertension.

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**Figure Legend:**

Different aspects of Irving Page's mosaic theory of hypertension revisited in this compendium. The 4 black elements are the principal components mentioned in the original 1949 paper (1). The 8 blue components are enumerated in the subsequent, more extensive revisiting of the theme in 1982 (2). The 8 red components are themes dealt with by review papers in the present Theme Issue of the Canadian Journal of Cardiology.